Monoclonal antibody Rituximab for severe immune thrombocytopenia after pegylated interferon for hepatitis C infection

Papakonstantinou I[1], Poulakidas I[2]

[1]1st Department of Internal Medicine
[2]Hematology Division
401 General Military Hospital of Athens, Greece

Abstract
Background: Severe immune thrombocytopenia displays a rare side effect of pegylated interferon therapy for Hepatitis C infection. Our aim is to report a case of severe and late onset immune thrombocytopenia due to pegylated interferon treatment that was effectively managed with the anti-CD20 monoclonal antibody Rituximab.
Description of the case: A 27-year-old male, Hepatitis C infected patient, presented with sudden, severe immune thrombocytopenia at the end of a standard 24-week antiviral treatment, as a side effect of pegylated interferon. Platelet count rapidly normalized with Rituximab infusions.
Conclusion: Rituximab could be a valuable treatment option in pegylated interferon related immune thrombocytopenia, when patients are resistant to conventional treatment or when physicians are reluctant to administer corticosteroids. Hippokratia 2014; 18 (4): 370-372.

Introduction

Thrombocytopenia is a common haematological abnormality diagnosed in patients affected with hepatitis C virus (HCV), and as well as an expected side effect of pegylated interferon (PEG-INF) treatment[1,2]. Nevertheless, severe immune thrombocytopenia (platelets <25,000/μL) is a rare side effect of PEG-INF[2]. The pathogenic mechanism possibly involves an interaction between platelets, antigen-presenting cells, T and B cells, evolving after the drug-dependent antibodies are directed against prevalent glycoproteins of the platelets' surface. This event signals the CD4+ T helper cells activation, and eventually the B-cell differentiation and autoantibody production that opsonize platelets, promoting phagocytosis[3,4]. Treatment of immune thrombocytopenia associated with PEG-INF therapy can be achieved with the monoclonal antibody Rituximab, that raises platelet counts in patients with immune thrombocytopenia by depleting the CD20-positive auto-reactive antibody-producing B cells[5,6].

Description of case

The patient reported is a 27-year-old male, who was diagnosed with HCV infection, after he was found on routine laboratory evaluation to have elevated aminotransferases. Anti-HCV antibodies in serum were positive and reverse transcriptase polymerase chain reaction (PCR) detected the HCV-RNA. The analysis of HCV-RNA revealed that the patient was infected with genotype 3a. Baseline platelet counts were within the lower normal limits; neutrophil counts, hematocrit, coagulation and other biochemical markers were normal. Liver biopsy showed mild histologic changes of chronic viral hepatitis and absence of significant fibrosis. The patient was treated with PEG-INF (180 μg sc weekly) and ribavirin (800 mg daily) for a total of 24 weeks[7]. After treatment completion, circulating HCV RNA was undetectable.

During the 24 weeks of therapy the patient developed thrombocytopenia with platelets around 80,000/μL that remained at this level, without any other side effects or autoimmune disorders. At the time the treatment was discontinued, severe thrombocytopenia, as low as 4,000/μL presented, without hemorrhagic manifestations (Figure 1). Secondary causes of thrombocytopenia (lymphoproliferative, autoimmune, thyroid disorders) were excluded by laboratory evaluation and bone marrow examination that was suggestive of peripheral platelets destruction[8]. An impending immunologic mechanism, as a late onset complication of PEG-INF, was assumed to be responsible. We infused, as first line treatment, high dose immunoglobulins (400 mg/kg) for five consecutive days, with no efficacy. We did not attempt to use corticosteroids. Then, the anti-CD20 monoclonal antibody Rituximab (375 mg/m^{2} weekly for 4 weeks), was administered[6]. After Rituximab infusion, the platelet count gradually normalized (Figure 1). The patient responded completely, did not present any other complications as result of treat-
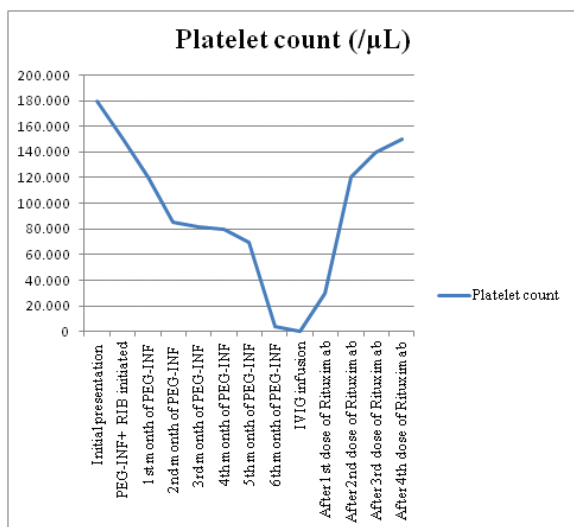
Figure 1: Changes in platelets values during antiviral therapy and therapeutic manipulations. Severe thrombocytopenia (platelets as low as 4,000/μL) presented at the time that the pegylated interferon plus ribavirin (PEG-INF+RIB) treatment was completed. At this point the patient had undetectable HCV-RNA. Intravenous immunoglobulins administered initially followed by Rituximab weekly infusions.

PEG-INF: pegylated interferon, RIB: ribavirin, IVIG: intravenous immunoglobulins.

ment or Hepatitis C, and he was not re-admitted to the hospital.

Discussion

This report is of interest in certain aspects. It describes a case of immune thrombocytopenia due to PEG-INF treatment for Hepatitis C, with extremely low platelet counts, that occurred during treatment completion. In a large cohort of 979 HCV-infected patients treated with PEG-INF, severe thrombocytopenia defined as a platelet count of less than 50,000/μL was reported overall in 6.1% and only two patients had nadir platelet counts of <10,000/μL[9]. In this study the incidence of severe thrombocytopenia after the 24 week of PEG-INF treatment ranged from 0.3-2.5% depending on the pre-treatment platelet counts[9].

We are aware of four case reports that described immune thrombocytopenia at the end of antiviral therapy for HCV (either with common IFN-α or PEG-INF) or during antiviral therapy for more than six months[5,10-12]. Also one case report described immune thrombocytopenia after 6 months from the PEG-INF discontinuation[13]. Rituximab was used and adequately restored platelet count only in one case[5], whereas in all other cases corticosteroids were administered[10-13].

Although Rituximab is considered to be a more intense immunosuppressive regimen compared to steroids, with no objective difference in timing of platelets response and the potential harmful outcome to induce virus replication[14], we did not use corticosteroids as the indicated first line treatment[8]. Despite the high initial therapeutic efficacy,

steroids achieve durable response in only 20-30%, often requiring ongoing or repeated administrations to maintain platelet counts, compared up to 50-70% therapeutic activity of Rituximab[6,8]. Our patient was debilitated from his previous treatment and could not tolerate a further long course of additional modalities. We also took into account that B-lymphocyte recovery occurs in 6–8 months after Rituximab infusion[15] and liver-related effects of rituximab-containing regimens on HCV-positive CD20-positive B-cell Lymphoma patients, in most cases are not followed by major clinical events[16].

In conclusion, this report underlines the significant response to anti-CD20 monoclonal antibody Rituximab, of a patient with severe PEG-INF related immune thrombocytopenia. In this context, physicians could be aware of anti-CD20 therapy as an alternative and efficacious option. From newer concepts, anti-CD20 treatment works by normalizing faulty T-cell responses, maintaining autoreactive T-cell activation and actually by restoring the defective tolerance-inducing to self antigens regulatory T cells that are essential in preventing autoimmunity[3,4,17].

Conflict of interest

Authors report no conflict of interest.

References

1. Louie KS, Micallef JM, Pimenta JM, Forssen UM. Prevalence of thrombocytopenia among patients with chronic hepatitis C: a systematic review. J Viral Hepat. 2011; 18: 1-7.
2. Roomer R, Hansen BE, Janssen HL, de Knegt RJ. Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. J Hepatol. 2010; 53: 455-459.
3. Cines DB, Liebman H, Stasi R. Pathobiology of secondary immune thrombocytopenia. Semin Hematol. 2009; 46: S2- S14.
4. Chong BH. Primary immune thrombocytopenia: understanding pathogenesis is the key to better treatments. J Thromb Haemost. 2009; 7: 319-321.
5. Weitz IC. Treatment of immune thrombocytopenia associated with interferon therapy of hepatitis C with the anti-CD20 monoclonal antibody, rituximab. Am J Hematol. 2005; 78: 138-141.
6. Zaja F, Volpetti S, Chiozzotto M, Puglisi S, Isola M, Buttignol S, et al. Long-term follow-up analysis after rituximab salvage therapy in adult patients with immune thrombocytopenia. Am J Hematol. 2012; 87: 886-889.
7. European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2014; 60: 392-420.
8. Neunert C, Lim W, Crowther M, Cohen A, Solberg L Jr, Crowther MA; American Society of Hematology. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011; 117: 4190-4207.
9. Hermos JA, Quach L, Gagnon DR, Weber HC, Altincatal A, Cho K, et al. Incident severe thrombocytopenia in veterans treated with pegylated interferon plus ribavirin for chronic hepatitis C infection. Pharmacoepidemiol Drug Saf. 2014; 23: 480-488.
10. Medeiros BC, Seligman PA, Everson GT, Forman LM. Possible autoimmune thrombocytopenia associated with pegylated interferon-alpha2a plus ribavarin treatment for hepatitis C. J Clin Gastroenterol. 2004; 38: 84-86.
11. Dimitroulopoulos D, Dourakis SP, Xinopoulos D, Tsamakidis K, Paraskevas E. Immune thrombocytopenic purpura in a patient treated with interferon alfacon-1. J Viral Hepat. 2004; 11: 477-478.
12. Jiang W, Hidaka H, Nakazawa T, Kitagawa H, Koizumi W. Se-

vere thrombocytopenia in a patient with inosine triphosphatase (ITPA)-CC genotype caused by pegylated interferon (IFN)-α-2a with ribavirin therapy: a case report. BMC Res Notes. 2014; 7: 141.

13. Elefsiniotis IS, Pantazis KD, Fotos NV, Moulakakis A, Mavrogiannis C. Late onset autoimmune thrombocytopenia associated with pegylated interferon-alpha-2b plus ribavirin treatment for chronic hepatitis C. J Gastroenterol Hepatol. 2006; 21: 622-623.

14. Sagnelli E, Pisaturo M, Sagnelli C, Coppola N. Rituximab-based treatment, HCV replication, and hepatic flares. Clin Dev Immunol. 2012; 2012: 945950.

15. Cooper N, Stasi R, Cunningham-Rundles S, Feuerstein MA, Leonard JP, Amadori S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenia. Br J Haematol. 2004; 125: 232-239.

16. Marignani M, Mangone M, Cox MC, Angeletti S, Veggia B, Ferrari A, et al. HCV-positive status and hepatitis flares in patients with B-cell non-Hodgkin's lymphoma treated with rituximab-containing regimens. Dig Liver Dis. 2011; 43: 139-142.

17. Stasi R, Cooper N, Del Poeta G, Stipa E, Laura Evangelista M, Abruzzese E, et al. Analysis of regulatory T-cell changes in patients with idiopathic thrombocytopenic purpura receiving B cell-depleting therapy with rituximab. Blood. 2008; 112: 1147-1150.